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Accelerated Partial Breast Irradiation for Breast Cancer: A Meta-Analysis[1]

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Abstract

To evaluate the long-term effect of breast conservation with accelerated partial breast irradiation (APBI) for early-stage breast cancer, PubMed, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Literature Database, Chinese Scientific Journals Full-text Database, and China Journal Full-text Database were searched to identify relevant original published trials. Randomized controlled trials in any language comparing APBI with whole-breast radiotherapy in patients with early-stage breast cancer were included. RevMan 5 software was used for statistical analysis. Four trials involving 919 patients were included. The rate of 5- and 7-year excellent/good cosmetic results was significant {odds ratio (OR) = 2.09 [95% confidence interval (CI) = 1.21-3.62]} between two groups. The 5- and 8-year overall survival had no significant difference [OR = 1.76 (95% CI = 0.67-4.62) and OR = 0.86 (95% CI = 0.44-1.66)]. The 10-year overall survival had significant differences [OR = 0.56 (95% CI = 0.35-0.91)]. There were no differences in the 5-year local recurrence (LR)–free survival [OR = 0.65 (95% CI = 0.18-2.34)], cancer-specific survival [OR = 1.67 (95% CI = 0.39-7.12)], disease-free survival [OR = 0.84 (95% CI = 0.38-1.84)], LR [OR = 1.36 (95% CI = 0.46-3.99)], the rate of contralateral breast cancer [OR = 2.82 (95% CI = 0.73-10.89)], and distant metastasis [OR = 0.71 (95% CI = 0.22-2.31)]. APBI significantly improved the rate of excellent/good cosmetic results anywhere in the breast, shortened the treatment time, alleviated the pain, and improved the quality of life. Future large-scale, high-quality, and double-blind trials are needed.

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Introduction

Breast-conserving surgery (BCS) and radiotherapy of the conserved breast have become widely accepted for the treatment of early-stage breast cancer. The main advantage of breast-conserving therapy is the excellent cosmetic outcome with less psychologic trauma compared with mastectomy. BCS followed by adjuvant to the whole-breast radiotherapy (WBRT) is the standard treatment for early-stage breast cancer in United Kingdom now. At the present, the standard WBRT technique after BCS is to treat the whole breast up to a total dose of 45 to 50 Gy, with or without a tumor bed boost [1–3]. However, about one third of women will develop acute skin toxicity after whole-breast irradiation for the high occurrence of acute moist dermatitis and the incidence of edema and hype pigmentation.

Many clinical trials have shown that breast intensity-modulated radiotherapy (IMRT) is a new technique. The use of IMRT for the treatment of the whole breast yields a significant decrease of the occurrence of acute moist dermatitis and the incidence of edema and hype pigmentation compared with WBRT, improves the quality of the life, reduces psychologic burden, and improves cosmetic effect [4–7].

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However, the major disadvantage of standard WBRT or IMRT is that it usually needs about 5 to 7 weeks. In other series, 15% to 30% of women treated with BCS failed to receive radiation therapy (RT) [8–10]. The reasons for the underuse of this treatment include patient convenience, physician preference, and logistical problems [10,11]. Accelerated partial breast irradiation (APBI) is an attractive treatment that needs only 1 to 2 weeks. The acceleration of RT would eliminate some of the disadvantages of the extended treatment period, especially for elderly patients. In addition, most local recurrences (LRs) occur in close proximity to the tumor bed [12,13].

We conducted a meta-analysis to assess the effect of APBI in patients with early-stage breast cancer after BCS.

Methods

Inclusion and Exclusion Criteria

All randomized controlled trials (RCTs), published and unpublished, were eligible for this meta-analysis. All the trials that compared APBI *versus* conventional WBRT in patients with early-stage breast cancer were eligible. The control group received WBRT; the treatment group received APBI. Planned conventional radiotherapy was 40 to 60 Gy for 5 to 6 weeks. Primary outcomes were response rate of excellent/good cosmetic results, the 5- and 8-year overall survival, the 10-year overall survival, the 5-year LR-free survival, cancer-specific survival, disease-free survival, LR, the rate of contralateral breast cancer and distant metastasis.

Literature Search

PubMed (1966-June 2013), Cochrane Library (Issue 3, 2008), EMBASE (1974-June 2013), Web of Science (1974-June 2013), Chinese Biomedical Literature Database (1978-June 2013), Chinese Scientific Journals Full-text Database (1989-June 2013), and China Journal Full-text Database (1997-June 2013) were independently searched in duplicate to identify all published (manuscripts and abstracts) RCTs that compared APBI *versus* conventional WBRT in patients with early-stage breast cancer. Manual searches were done by reviewing articles and abstracts cited in the reference lists of identified RCTs. In addition, abstracts published in the Proceedings of the Annual Meetings of the American Society of Clinical Oncology (through 2012) were systematically searched for evidence relevant to this meta-analysis. There were no language and date restrictions.

The following search terms were used: 1) breast neoplasm, breast tumor, human mammary carcinoma, human mammary neoplasm, and breast cancer; 2) accelerated partial breast irradiation; 3) segmental mastectomy, partial mastectomy, limited resection mastectomy, lumpectomy, local excision mastectomy, and breast-conserving surgery; and 3) clinical trial phase III and randomized controlled trials. The searches were done by integrating Mesh heading [MEDLINE (Mesh), EMBASE (EMTREE)] and with text words. All the searched abstracts were screened for relevance. The selection of studies for inclusion was carried out independently by two individuals.

Data Extraction and Quality Assessment

Data was extracted by Ye and Bao. The results were compared, and disagreements were resolved by consensus. Each study was evaluated for quality by two reviewers using the following Quality Assess Criteria of RCT: 1) randomized method, 2) allocation concealment, 3) blindness to whether it was adapted, and 4) with or without lost follow-up (if it has been lost to follow-up, whether with analysis in intention to treat) [14]. If only one criterion was satisfied, the bias of trials was moderate. If none of the criteria was satisfied, the bias was severe. In addition, we analyzed the baseline information and status of patients to judge the practice bias. If reviewers disagreed with the quality assessment, discrepancies were identified, and a consensus was reached.

Data Analysis and Statistical Methods

We analyzed, extracted, and pooled data using Review Manager 5.0 (The Nordic Cochrane Centre, Copenhagen, Denmark) for summary estimate [15]. Dichotomous outcomes of standard mean were expressed as risk ratios with 95% confidence intervals (CIs). The w^2 statistic was used to assess heterogeneity between trials, and

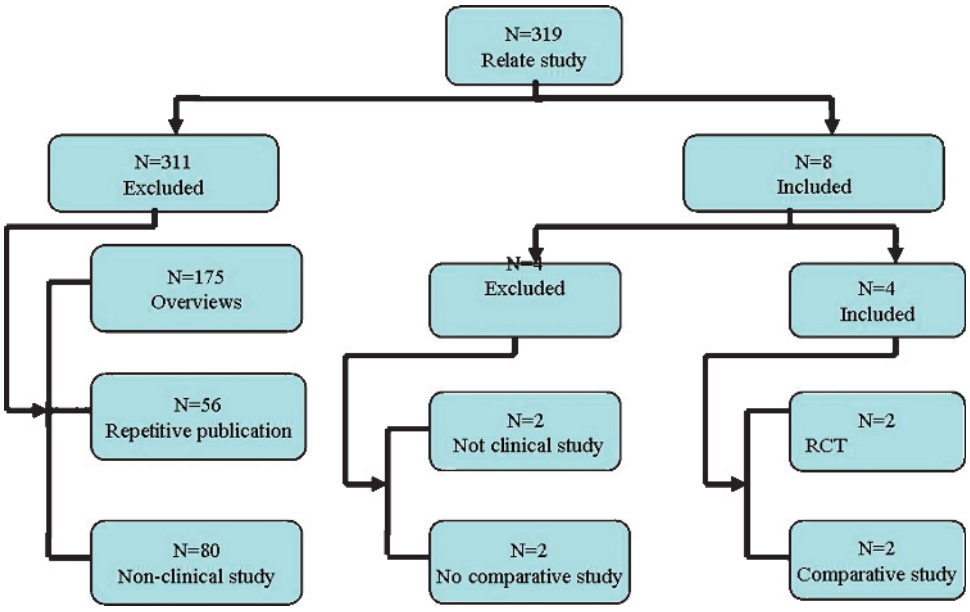

Figure 1. Flow chart of the studies.

Table 1. Characteristics of Randomized Controlled Trials Included in this Meta-Analysis.

Study (year)	Case No. (APBI/WBRT)	Age		Mean Tumor Size(mm; range)		Intervention		Outcome Measurement
		APBI	WBRT	APBI	WBRT	APBI	WBRT	
Dodwell DJ et al. (2005)	84/90	25-69	23-68	19 3-45	21 5-45	55 Gy/20 × 2.75 Gy/4 w	40 Gy/15 × 2.67 Gy/21 d + 15 Gy/5 × 3 Gy	The 8-year overall survival, distant metastasis, LR
Polgár C et al. (2007)	128/130	30-84	31-80	13 1-20	13 1-20	High-dose rate (HDR) 36.4 Gy/7 × 5.2 Gy/4 d	50 Gy/25 × 2 Gy/5 wk (42-50 Gy)	The 5-year overall survival, LR-free survival, cancer-specific survival, disease-free survival, distant metastasis–free survival, LR rate, the rate of excellent/good cosmetic results, the contralateral breast cancer rate, distant metastasis rate
Antonucci JV et al. (2009)	199/199	40-90	38-90	12 1-20	13 1-20	Low-dose-rate (LDR), 50 Gy for 96 h at 0.52 Gy/h (120) (HDR) 32 Gy/ 8 × 4 Gy or 34 Gy /10 × 3.4 Gy/5 d (79)	60 Gy/30 × 2 Gy/6 wk	The 10-year overall survival, LR-free survival, cancer-specific survival, disease-free survival, distant metastasis–free survival, LR rate, the rate of excellent/good cosmetic results, the contralateral breast cancer rate, distant metastasis rate, the ipsilateral breast recurrence rate
Major T et al (2004)	45/44	38-78	34-78	12 1-20	13 1-20	(HDR) 30.3 Gy/7 × 4.3 Gy or 36.4 Gy/7 × 5.2 Gy/4 d	50 Gy/25 × 2 Gy/5 wk	The 5-year LR rate, the 7-year LR-free survival, cancer-specific survival, the ipsilateral breast recurrence rate, the rate of excellent/good cosmetic results, the grade 2 or worse late radiation side effects

the I^2 statistic was used to assess the extent of inconsistency [16]. A fixed-effect model was used for calculations of summary estimates and their 95% CI, unless there was significant heterogeneity, in which case results were confirmed using a random-effects statistical model. Sensitivity analysis was performed by excluding the trials in which quality was very poor or there existed a significant clinical heterogeneity. Publication bias is a common concern in meta-analysis that is related to the tendency of journals to favor the publication of large and positive studies.

Results

We obtained 319 potentially eligible publications after six articles were excluded when reading title and abstract, for these six articles were irrelevant with our study. Figure 1 showed the flow chart of the studies. Four RCTs [17–20] with 919 patients were used for this meta-analysis.

Table 1 showed the characteristics of patients and treatment in the included trials [17–20]. APBI modalities varied between the trials in terms of study, sample, outcome indexes, as well as quality assessment. Thus, there were no significant differences in main characteristics between groups.

Methodological Quality of Included Studies

The specific information on study design was shown in Table 2 [17–20]. Each included RCT as assessed for quality using the validated quality assessment criteria of RCT [15]. Only one [17] of the four studies pointed out that randomization was done with computer-generated method and used a single-blind trial and described the allocation concealment. One study did not describe the randomization. Two studies are clinical trials; the allocation concealment of the three trials was unclear.

Meta-Analysis

Overall survival. Three trials [17,19,20] reported the 5-, 8-, and 10-year overall survival rate. There were no differences statistically between APBI and WBRT in 5-year overall survival rate [odds ratio (OR) = 1.76 (95% CI = 0.67-4.62), $P = .25$] and 8-year overall survival rate [OR = 0.86 (95% CI = 0.44-1.66), $P = .65$], but there was statistical difference in 10-year overall survival rate [OR = 0.56 (95% CI = 0.35-0.91), $P = .02$] (Figure 2).

LR-free survival. Two trials [17,18] reported the 5- and 7-year LR-free survival rate. There were no differences between APBI and WBRT in 5-year LR-free survival rate [OR = 0.65 (95% CI = 0.18-2.34), $P = .51$] and 7-year LR-free survival rate [OR = 1.33 (95% CI = 0.49-3.62), $P = .57$] (Figure 3).

Cancer-specific survival. Three trials [17–19] reported the 5-, 7-, and 10-year cancer-specific survival rate. There were no differences between APBI and WBRT in 5-year cancer-specific survival rate [OR = 1.67 (95% CI = 0.39-7.12), $P = .49$], 7-year cancer-specific survival rate [OR = 1.40 (95% CI = 0.29-6.65), $P = .67$], and 10-year cancer-specific survival rate [OR = 1.43 (95% CI = 0.62-3.30), $P = .40$] (Figure 4).

Disease-free survival. Two trials [17,19] reported the 5- and 10-year disease-free survival rate. There were no differences between APBI and WBRT in 5-year disease-free survival rate [OR = 0.84

Table 2. Quality Assessment of Randomized Controlled Trials Included in this Meta-Analysis.

Study (year)	Randomization	Allocated Concealment	Blinding	Loss of Follow-up	Selective Outcome Reporting	Other Potential Threats to Validity
Dodwell DJ et al. (2005)	Unclear	Unclear	Unclear	No	Unclear	Unclear
Polgár C et al. (2007)	Compute	Adequate	Single-blind	No	Unclear	Unclear
Antonucci JV et al. (2009)	Unclear	Unclear	Unclear	No	Unclear	Unclear
Major T. et al. (2004)	Unclear	Unclear	Unclear	No	Unclear	Unclear

(95% CI = 0.38-1.84), P = .66], but there was difference in 10-year disease-free survival rate [OR = 0.63 (95% CI = 0.41-0.99), P = .04] (Figure 5).

The rate of excellent/good cosmetic results. Two trials [17,18] reported the 5- and 7-year excellent/good cosmetic rate. There were differences between APBI and WBRT in 5-year excellent/good cosmetic rate [OR = 2.09 (95% CI = 1.21-3.62), P = .009] and 7-year excellent/good cosmetic rate [OR = 3.42 (95% CI = 1.25-9.38), P = .02] (Figure 6).

LR rate. Two trials [17,18] reported the 5-year LR rate. There were no differences between APBI and WBRT in 5-year LR rate [OR = 1.36 (95% CI = 0.46-3.99), P = .58]. Tests for heterogeneity in the analysis were not statistically significant (P = .70). Two trials [19,20] reported the 8- and 10-year LR rate. There were no differences between APBI and WBRT in 8-year LR rate [OR = 2.91 (95% CI = 0.87-9.65), P = .08] and in 10-year LR rate [OR = 1.26 (95% CI = 0.49-3.27), P = .63] (Figure 7).

The contralateral breast cancer rate. Three trials [17–19] reported the 5-, 7-, and 10-year contralateral breast cancer rate. There were no differences between APBI and WBRT in 5-year contralateral breast cancer rate [OR = 2.82 (95% CI = 0.73-10.89), P = .13], in 7-year contralateral breast cancer rate [OR = 0.19 (95% CI = 0.01-4.00), P = .28], and in 10-year contralateral breast cancer rate [OR = 0.48 (95% CI = 0.20-1.15), P = .10] (Figure 8).

Distant metastasis rate. Two trials [17,19] reported the 5- and 10-year distant metastasis rate. There were no differences between APBI and WBRT in 5-year distant metastasis rate [OR = 0.71 (95% CI = 0.22-2.31), P = .57] and in 10-year distant metastasis rate [OR = 0.53 (95% CI = 0.24-1.18), P = .12] (Figure 9).

The grade 2 or worse late radiation side effects. One trial [18] reported the 7-year grade 2 or worse late radiation side effects. There were no differences between APBI and WBRT in 7-year grade 2 or worse late radiation side effects [OR = 0.47 (95% CI = 0.08-2.68),

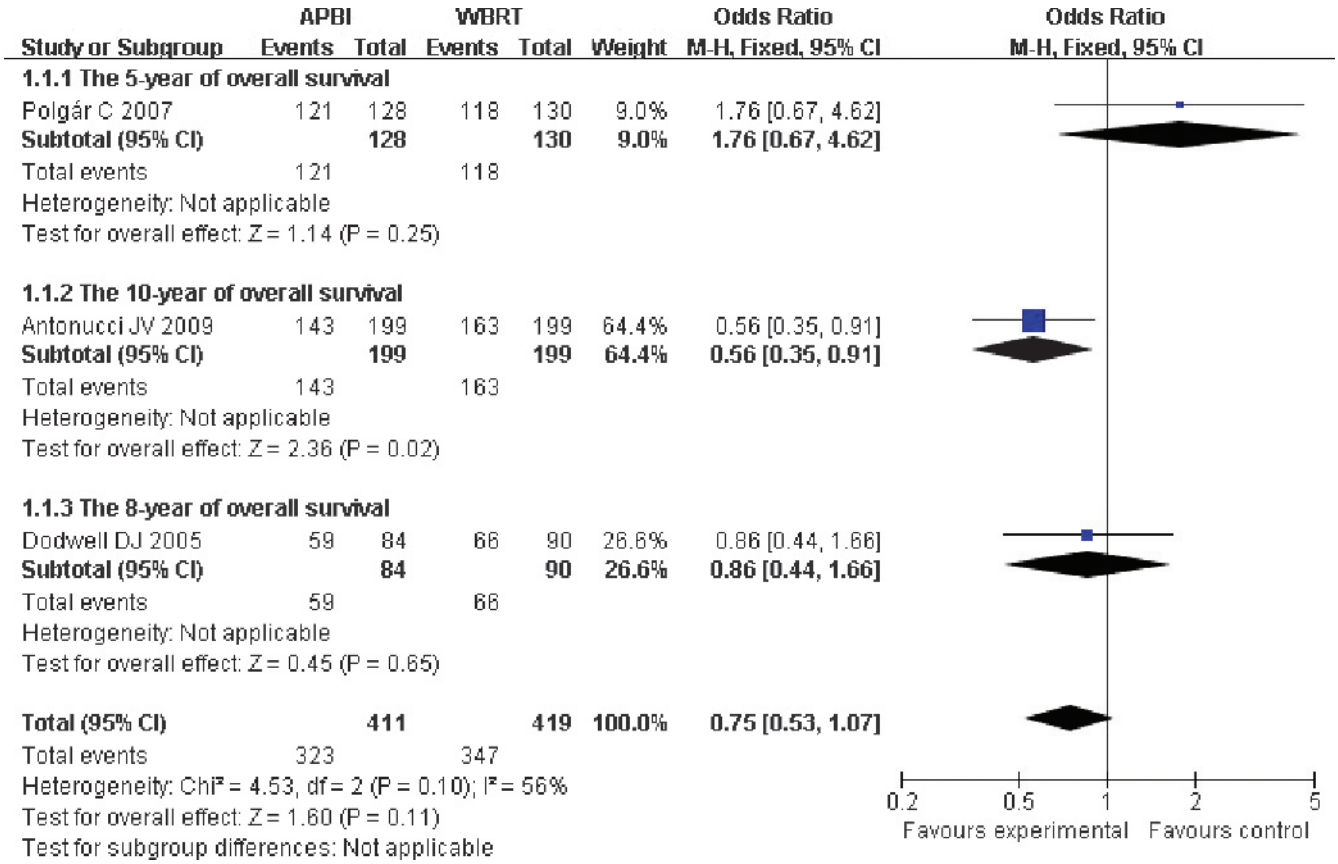

Figure 2. The 5-, 8-, and 10-year overall survival.

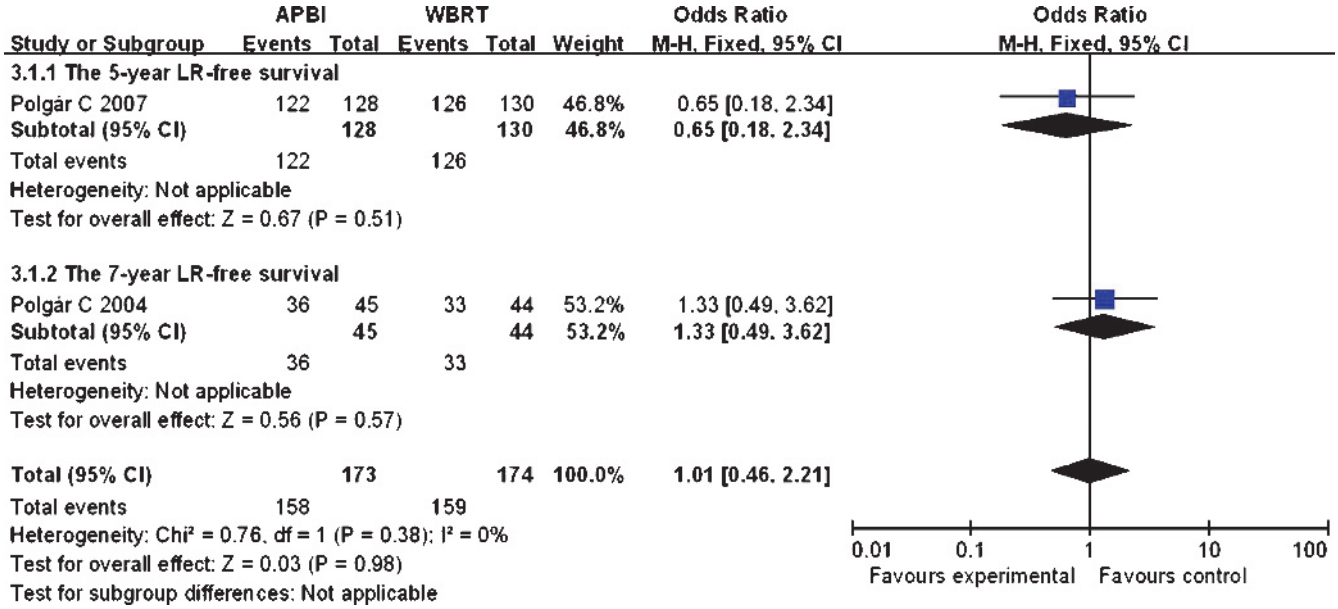

Figure 3. The 5-, 7-year LR-free survival.

P = .39] and in 7-year incidence of grades 2 to 3 fibrosis rate [OR = 3.42 (95% CI = 0.86-13.60), *P* = .08] (Figure 10).

Discussion

This meta-analysis showed the benefit of the APBI, but no subgroups have been able to unequivocally identify the use of ABPI that can be regarded as a safe and standard alternative to WBRT [21].

WBRT remains the golden standard for patients with BCS, but the rate of moist desquamation varies highly and prolongs the treatment time. One study [22] showed that 20% of women did not receive radiotherapy after BCS. It confirmed that age was really the reason to reduce the number of receiving radiotherapy. Many women undergoing RT to the whole breast may experience pain and discomfort by acute and chronic skin toxicity. The occurrences of edema and hype

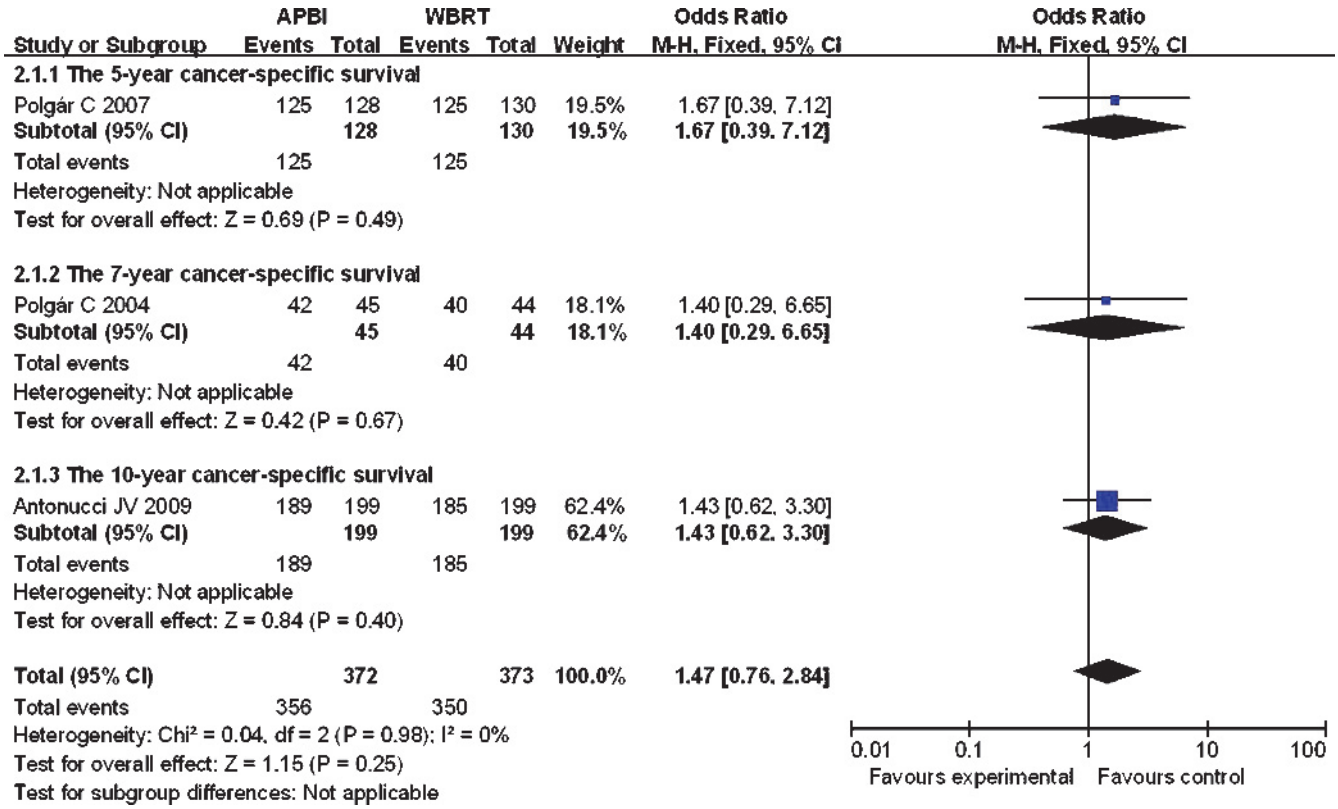

Figure 4. The 5-, 7-, and 10-year cancer-specific survival.

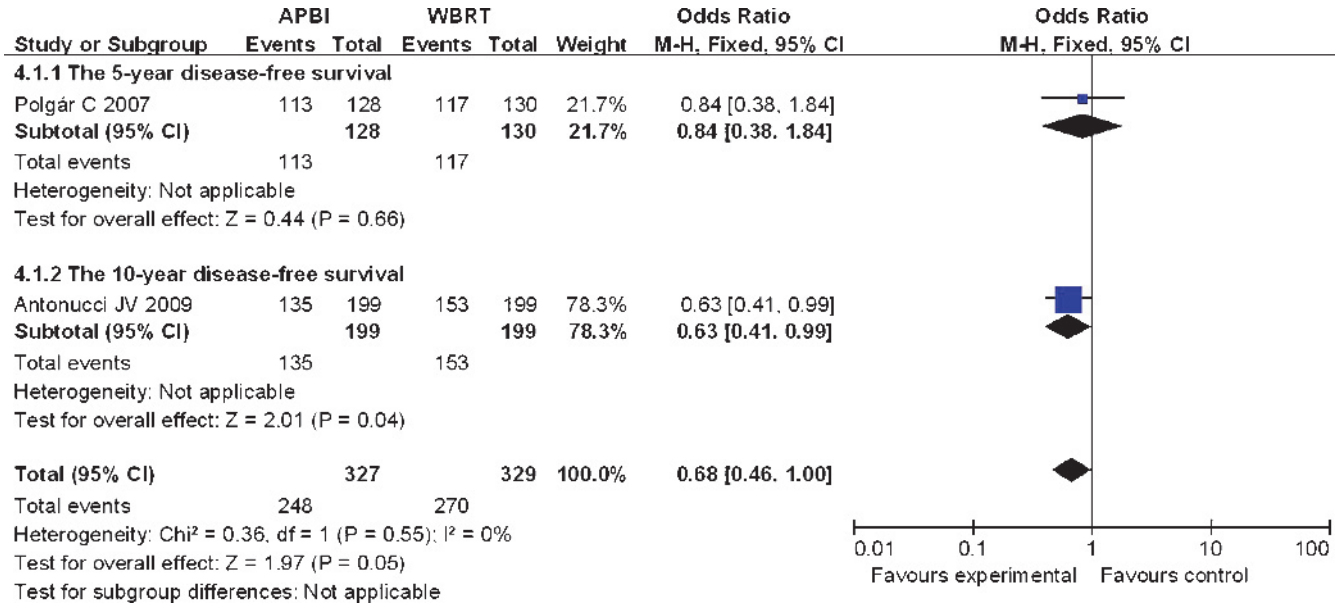

Figure 5. The 5- and 10-year disease-free survival.

pigmentation usually produce negative emotion. Therefore, recently, researchers have studied some new methods to reduce the therapeutic duration time, inconvenience, or toxicity.

The main advantage of ABPI is shortening of the treatment time, which is appealing especially when radiation resources are limited [21]. However, evidence from randomized trials of the benefits of these techniques is currently lacking.

In the present meta-analysis, we found that APBI was associated with a reduction in treatment time and good cosmetic result compared with WBRT. Our meta-analysis showed the dramatic improvement in good cosmetic result using breast APBI, and the 5- and 7-year absolute good cosmetic result was statistically significant compared with WBRT, APBI being respectively better than WBRT. It produced a significant 25% absolute improvement in good cosmetic results. The 5-, 7-, and 8-year overall survival, recurrence-free survival, cancer-specific survival, disease-free survival, LR rate, the incidence of contralateral breast cancer, and distant metastasis rate were not statistically significant. One study compared that the 10-year overall survival difference was statistically significant and WBRT was better than the APBI but the study included small sample size.

APBI is an attractive treatment that needs only 1 to 2 weeks. The acceleration of RT would eliminate some of the disadvantages of the extended treatment period, especially for elderly patients. The rationale for APBI is that the majority of LRs occur in close proximity to the tumor bed [12,23].

There are some benefits of breast APBI. Partial breast irradiation did not increase the risk of true recurrence or, elsewhere, breast failure. Significantly better cosmetic outcome can be achieved compared

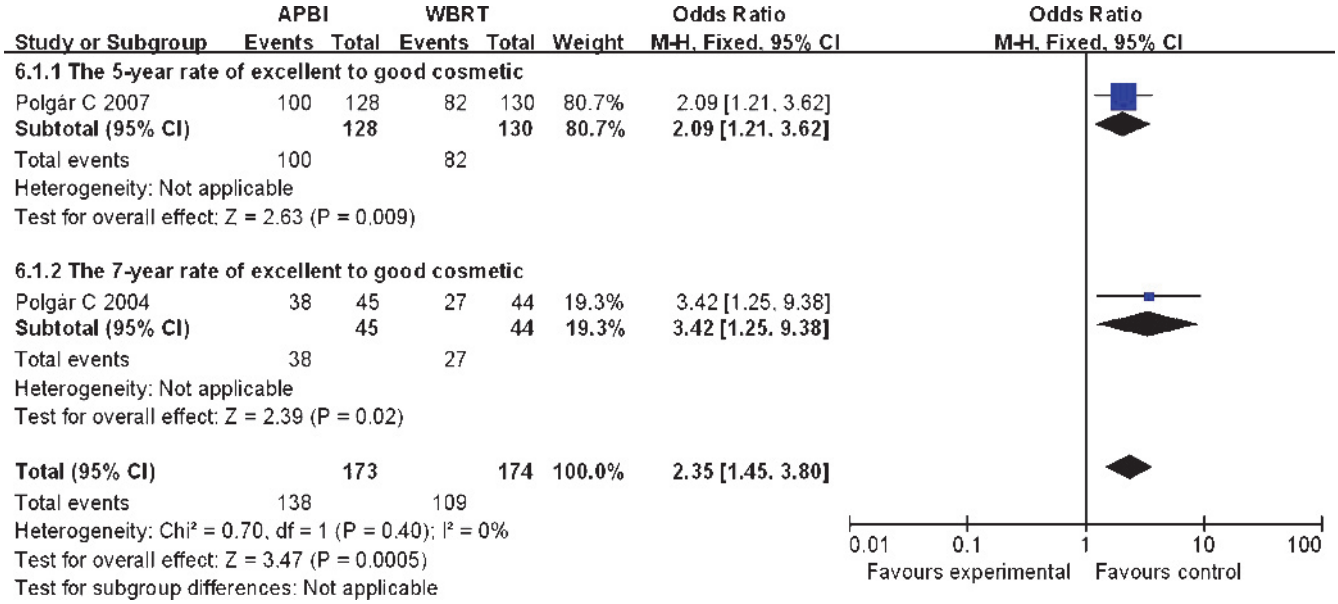

Figure 6. The 5- and 7-year excellent/good cosmetic results.

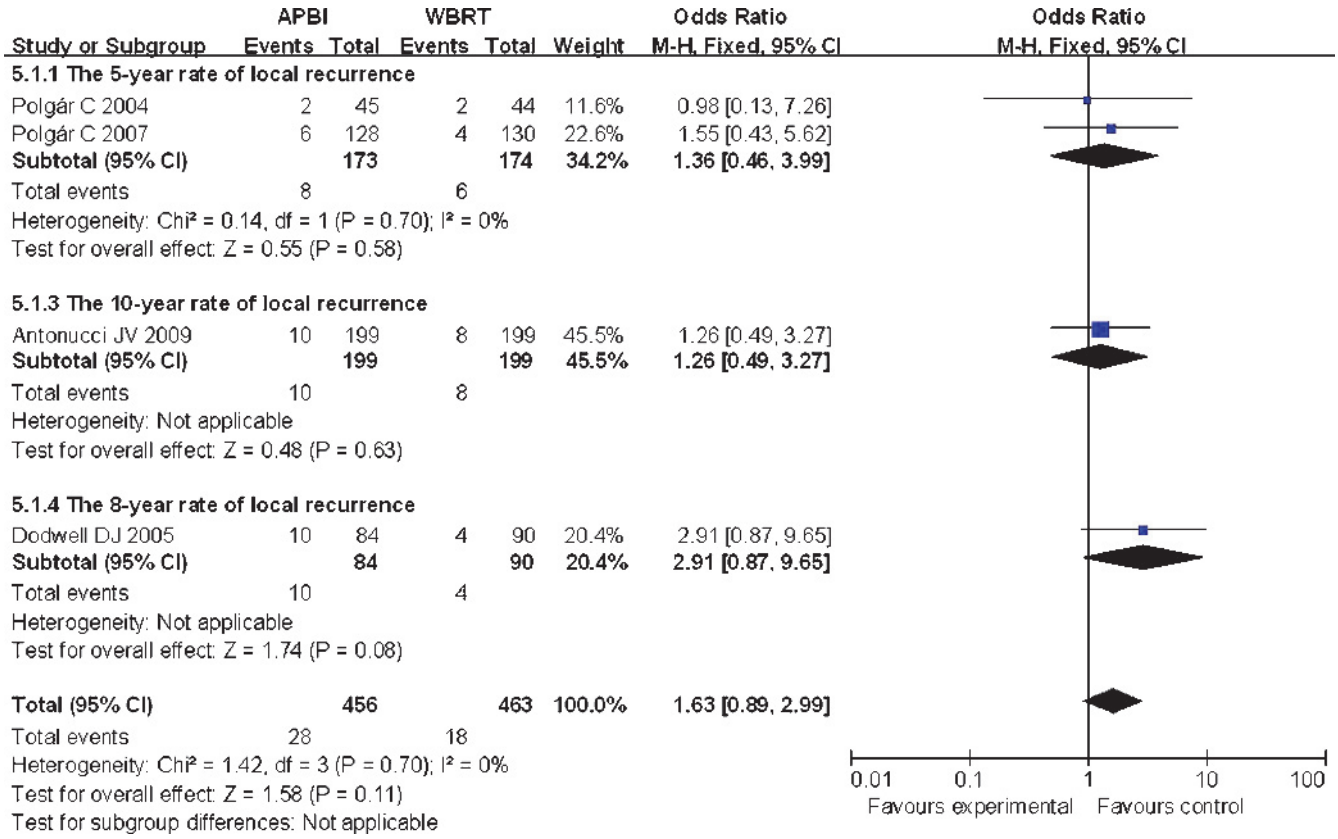

Figure 7. The 5-, 8-, and 10-year LR.

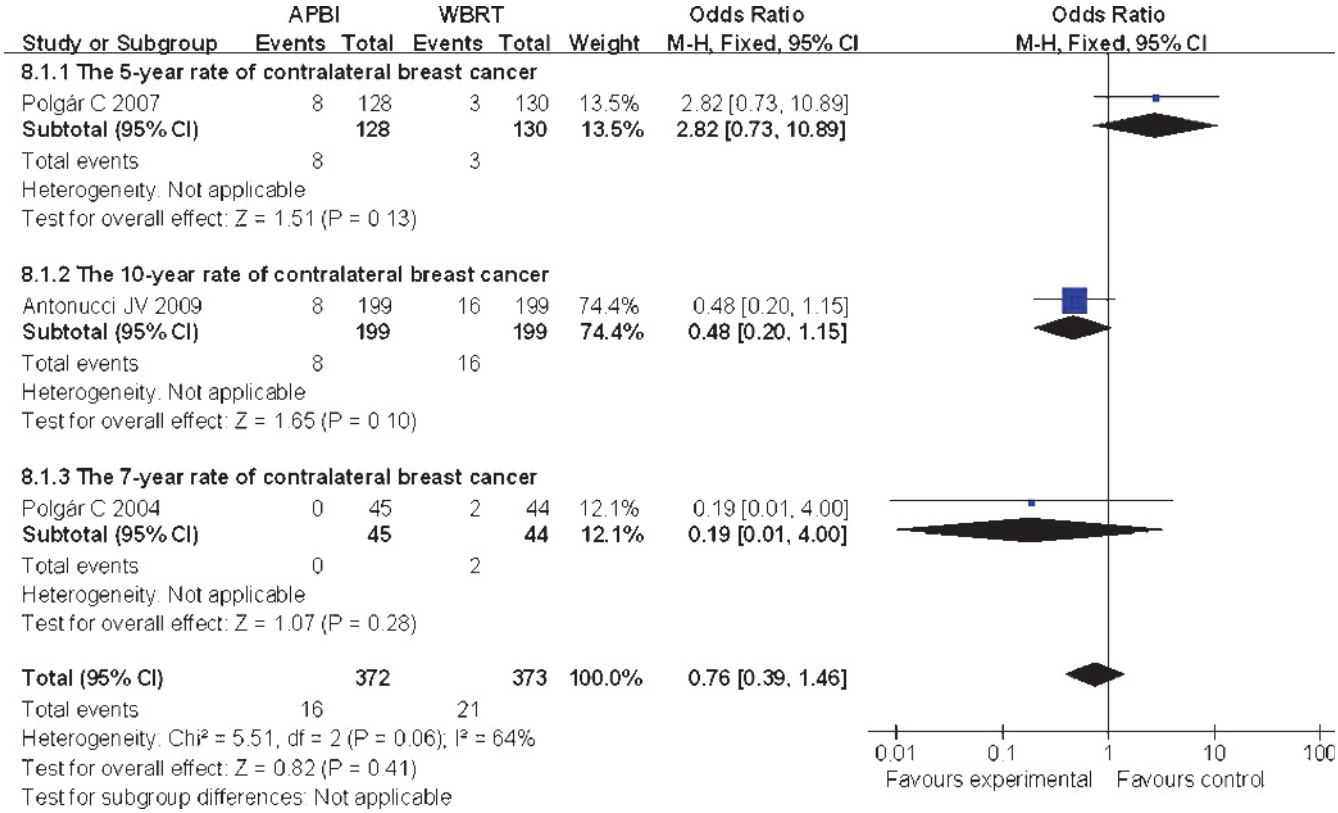

Figure 8. The 5-, 7-, and 10-year contralateral breast cancer.

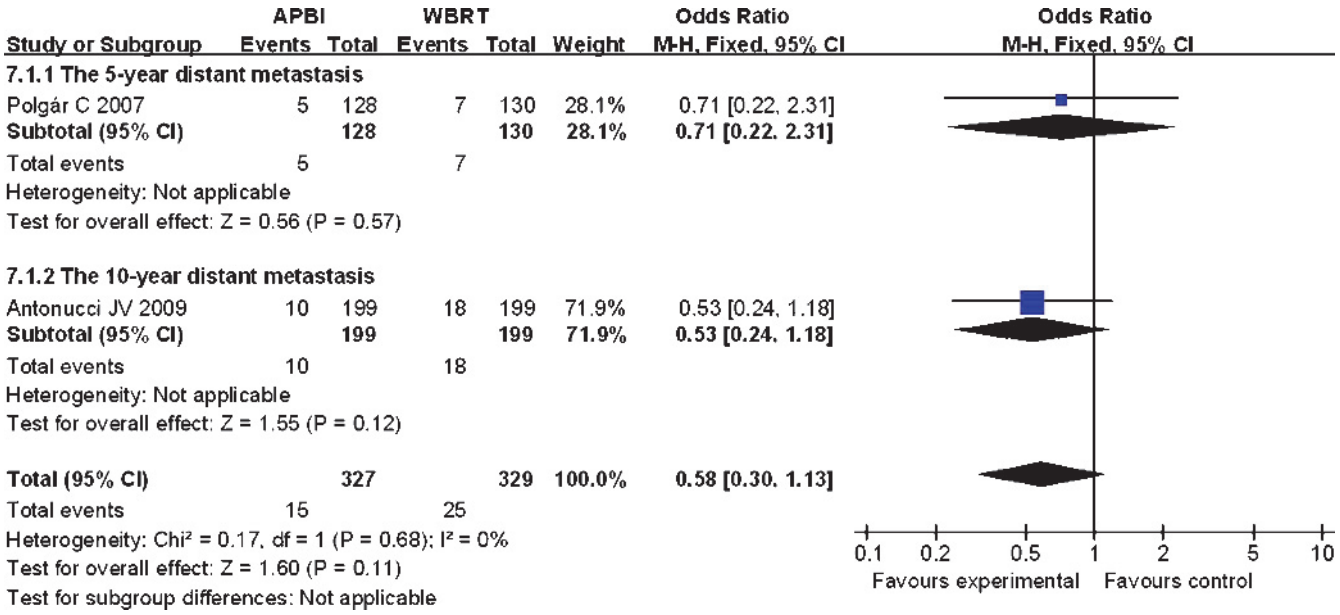

Figure 9. The 5- and 10-year distant metastasis.

with the outcome after WBRT. APBI shortens the period of treatment time in just only 1 to 2 weeks. APBI is only part of the breast irradiation reducing the target volume and lowering the incidence of skin toxic.

Due to different ways of radiotherapy, the skin toxicity and cosmetic results and complications must be concerned. King et al. [24] reported that the incidence of 1, 2 side effects was 22% using the implantation radiotherapy, complication rate was 8%, and level 3 (mainly fat necrosis) required surgery. The other obvious complications that impact on the cosmetic results were breast fibrosis and telangiectasia [25]. Most of researches [24–26] reported the satisfaction with cosmetic results more than 90% using APBI treatment.

The present study also had some limitations. First, meta-analysis based on published data that will overestimate treatment effects and contained very limited data might interfere with the results of the present study. Second, between the two treatment arms, the different RT techniques were allowed, and the statistical power might be limited for detection of small possible differences in local tumor control. Third, the quality of all trials included were not high; only one of the four studies pointed out that randomization was done with computer-generated method and used a single-blind trial, and the allocation concealment was clear. One study mentioned the randomization method, but blindness and the allocation concealment were all unclear. Otherwise, only four trials were included in our meta-analysis,

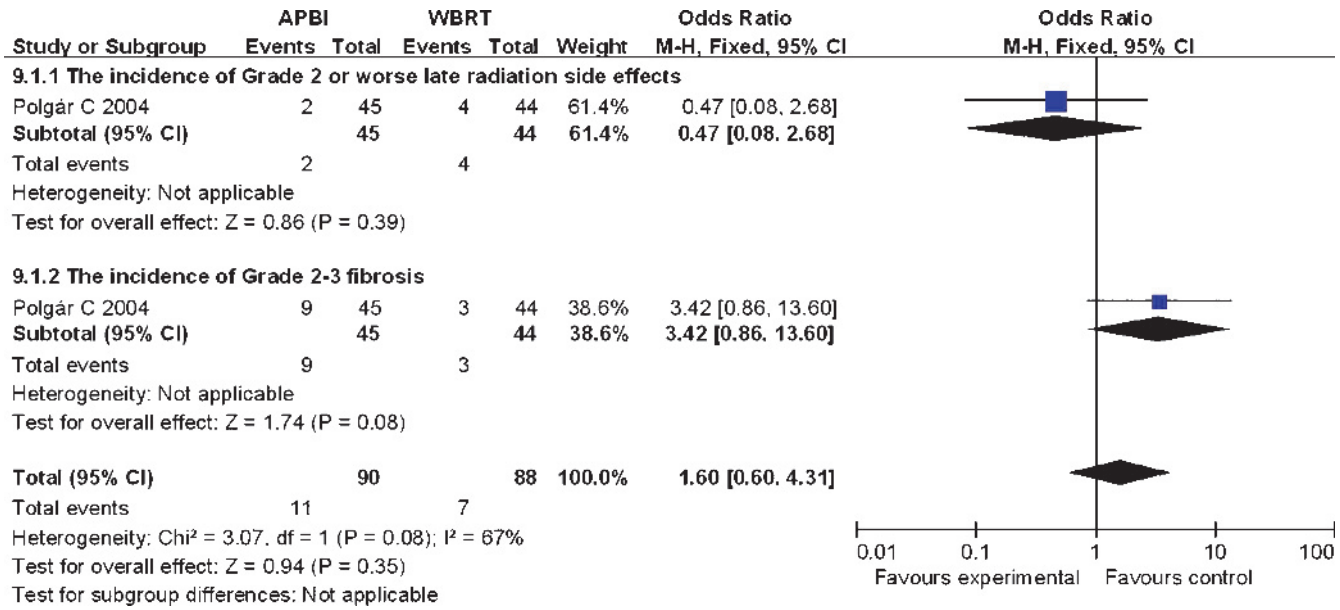

Figure 10. The 7-year grade 2 or worse late radiation side effects.

publication bias was inevitable, and therefore, we did not estimate publication bias with a funnel plot. So, we should interpret the results with care, especially for a positive result.

In conclusion, our analysis contained current available evidence showing that APBI has a better cosmetic result and shortens treatment time. The overall survival, recurrence-free survival, cancer-specific survival, disease-free survival, LR rate, the incidence of contralateral breast cancer, and distant metastasis rate were similar with WBRT. APBI techniques resulted in a significant reduction of the treatment time. A future study will focus on treatment time and improving the quality of life. It will be urgent for large randomized controlled studies of partial breast radiotherapy to be carried out to validate the safety and efficacy of these rapidly evolving technologies.

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